The AAPS Journal 2005; 7 (2) Article 36 (http://www.aapsj.org).

Themed Issue: Population Pharmacokinetics - In Memory of Lewis Sheiner
Guest Editors - Peter Bonate and Diane Mould

Population Pharmacokinetics: A Memorial Tribute to Lewis Sheiner

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PREFACE: SOME PERSONAL MEMORIES OF LEWIS SHEINER AND NONMEM

Diane Mould

It is difficult to write an introduction for a memorial issue, particularly for somebody like Lewis. Simply put, Lewis was an amazing person. I was never a fellow of his, much to my lasting regret. I feel sure that his fellows knew him far better than I ever did. And yet I did get to know him, as so many NONMEM users have over the years. Lewis was the quintessential educator. He loved a challenge and enjoyed solving problems. I think he enjoyed it even more if his students got the solution first.

I first encountered NONMEM as a graduate student at the Ohio State University. The University was running NONMEM Version III, and it required the user to painstakingly define the partial differentials of the function being evaluated. The input was "card image," requiring meticulous programming to merge the data and then achieve the appropriate format. Getting a model control stream and data ready to run took days of effort. I enjoyed helping debug the code and was fascinated at how much processor time it took to run–nearly as much as the molecular modeling software I had given up in favor of pharmacokinetic pursuits. Consequently, I heard a lot of complaints about what NONMEM was doing to the University computer system, but I had never heard of anybody called Lewis Sheiner.

Shortly afterward, I left graduate school and took a job in industry. Almost immediately, I was sent to University of California, San Francisco (UCSF) to take the advanced course in pharmacokinetics and pharmacodynamics. I finally met Lewis, and a whole new world was opened for me. Here was somebody who understood the potential applications of cellular automata for modeling cancer growth. He had a mind that was so bright and flexible that he understood what I asked even when I used engineering terminology to ask the questions. And he answered those questions in such a straightforward way that I understood the responses and learned what he had to teach.

Meanwhile, NONMEM had been upgraded to Version IV, which had NMTRAN. The addition of NMTRAN changed NONMEM from an esoteric piece of software to something that could be used by a much larger group of people. The new world that Lewis had opened up for me at UCSF had just had its horizons made much broader. NONMEM still slowed down the mainframe computer systems it was usually housed on, and I still heard a lot of complaints about that, but it was a challenging, demanding, and often frustrating puzzle that had me addicted. Over the years, I began to think that figuring out how to trick NONMEM into doing something was actually a lot more fun than developing the model itself. I corresponded with Lewis via email about different problems, as I am sure many others did. Lewis was generous with his time.

UCSF held intermediate NONMEM users workshops, where the users had an opportunity to discuss interesting problems, aspects of NONMEM, and had the chance to interact directly with Lewis. Lewis also contributed regularly to NMUSERS, the NONMEM "chat group," offering input and advice on a wide variety of discussions and answering users' questions. He believed in people, and he believed in science. We learned because he thought we could.

NONMEM V finally made its appearance, and we were able to utilize user-defined subroutines more easily. The estimation methods were improved so that users could implement the more robust methods with shorter run times. The number of complaints from other system users whose work was held up by NONMEM runs finally died away. More and more people began to install and run NONMEM on personal computers. NONMEM had become portable.

Lewis published an incredible number of articles. These articles were often preludes to the next wave of new modeling concepts that other users eagerly read, learned, and tried. Many users improved on his ideas, which I am certain pleased him. Lewis was interested in drug development as a process and set out to improve that process. He interacted with students, industry, and the regulatory authorities. He changed our world by integrating pharmacology with pharmacokinetics and by making rational dosing a realistic and realizable goal.

We are still anxiously awaiting the arrival of NONMEM VI. Rumor has it that we will be able to use stochastic differential equations. That means more for us to learn. Somehow, I am sure we will manage, even without our favorite teacher to guide us.

Lewis was amazing. He was interested in nearly anything, and I think he never stopped trying to learn. I enjoyed his

humor, his *joi de vivre,* and his mind. I liked him, and I still miss him. What is a greater tragedy is that there are so many people now who will never benefit from his teaching. We owe an enormous debt to Lewis for giving us a livelihood and a challenging livelihood at that. This issue was conceived partly to remember him but also in some small way give something back by helping to educate users and to expand the science that Lewis was best known for.

Peter Bonate

I never had the pleasure of meeting Dr. Sheiner one-on-one. I saw him only twice in professional settings: once at a Georgetown University conference on simulation and a second time some years later at a Food and Drug Administration Clinical Pharmacology Subcommittee meeting. The impact Dr. Sheiner had on clinical pharmacology is enormous. To say that he and his colleagues at UCSF created a revolution in pharmacokinetic analysis and drug development that continues to this day is not such a bold statement. It was clear by the early to mid-1980s that pharmacokinetic analysis was moving toward a reliance on noncompartmental methods, because there was a strong perception in the field that compartmental models were too dependent on the modeler's opinions and judgment and that noncompartmental methods were "model-independent" (which, perhaps, is a poor choice of words, because anyone who does this type of analysis knows that the user's judgment does play a role and that noncompartmental analysis does have certain assumptions). However, noncompartmental methods could not solve the problem of dealing with sparse pharmacokinetic data collected in phase III trials, and the results obtained could not be used in simulation. When population pharmacokinetics was introduced in 1977 and additionally developed in the early 1980s, there was great enthusiasm for the methodology but, because of computer restrictions (slow processor speeds and inaccessibility of computing time) and the user-unfriendliness of NONMEM, the method did not catch on except with a few individuals. As later versions of NONMEM were released that were more user friendly, coupled with the advances in personal computer processing speed and availability, population pharmacokinetics has truly taken off with an exponential increase in published papers seen in the last decade. Although Dr. Sheiner will be remembered for his contribution to population pharmacokinetics, his more lasting impact will be on quantitative pharmacology–making scientists realize that we should treat our data more quantitatively to answer specific questions instead of just summarizing our results into a few key components.